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ON the REARRANGEMENT of the TAUTOMERIC SALTS of 1,4,-DIPHENYL -5-THIONURAZOLE and 1,4,-DIPHENYL -5-THIOLURAZOLE.

DISSERTATION.

SUBMITTED TO THE BOARD OF UNIVERSITY STUDIES OF THE
JOHNS HOPKINS UNIVERSITY IN CONFORMITY
WITH THE REQUIREMENTS FOR THE DEGREE
OF DOCTOR OF PHILOSOPHY.

By

ERNEST P. DOETSCH.

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1911.

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ACKNOWLEDGMENT.

The author takes pleasure in expressing his gratitude to President Remsen, Professor Morse, Professor Jones, and Associate Professor Acree, for instruction in the lecture room and laboratory. Especial thanks are due Associate Professor Acree, under whose personal direction this investigation was made.

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THE REARRANGEMENT OF THE TAUTOMERIC SALTS OF 1,4,-DIPHENYL -5-THIONURAZOLE AND 1,4,-DIPHENYL-5-THIOLURAZOLE.

The study of the reactions of tautomeric compounds in which the equilibrium between the two tautomeric forms is established very rapidly in comparison with the velocity of the reaction in question has given results which conform very well with the ideas advanced by Acree and his coworkers.(1) The study of the same phenomena in cases in which the equilibrium between the two tautomeric forms is established at a rate comparable with the velocity of the reaction has also been studied by Nirdlinger and Acree,(2) and the theory here also seems to apply as well. The work previous to that of Nirdlinger was done on a purely qualitative basis and no attempt was made to study quantitatively the rearrangements of acids or salts, or of the alkylation products obtained from the salts or acids, or of the alkylation products of a mixture of acids or salts of any two tautomers.

Among the earliest observations of compounds showing dynamic isomerism were acetyl dibenzoyl methane, tribenzoyl methane and mesityl oxide oxalic ester, discovered by Claisen.(3) He obtained the first two compounds by the interaction of the sodium salt~~s~~ of benzoyl acetyl methane $C_6H_5COCH_2COCH_3$ and benzoyl

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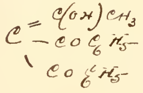
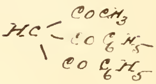
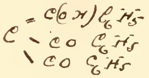
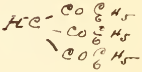
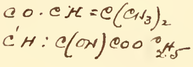
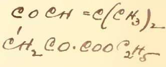
(1) American Chemical Journal, 37, 71; 38, 1; 39, 124; 39, 226.
(2) Ibid., 43, 219.
(3) Liebig's Annalen, 1893, 277-184; 1896, 291, 25.

chloride; the third compound was obtained from the condensation of mesityl oxide and oxalic ~~acid~~ ester in the presence of sodium ethylate. The formulae which represent the enol and keto forms, as given by Claisen, are:

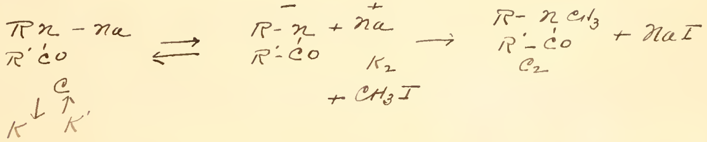
	Enol	Keto
Acetyl dibenzoyl methane:	 $C\begin{array}{l}=C(OH)CH_3\\-COC_6H_5\\\diagdown COC_6H_5\end{array}$	 $HC\begin{array}{l}\diagup COCH_3\\-COC_6H_5\\\diagdown COC_6H_5\end{array}$
Tribenzoyl methane:	 $C\begin{array}{l}=C(OH)C_6H_5\\\diagdown COC_6H_5\\\diagdown COC_6H_5\end{array}$	 $HC\begin{array}{l}\diagup COC_6H_5\\-COC_6H_5\\\diagdown COC_6H_5\end{array}$
Mesityl oxide oxalic ester:	 $\begin{array}{l}CO\cdot CH=C(CH_3)_2\\\vert\\CH:C(OH)COOC_2H_5\end{array}$	 $\begin{array}{l}COCH=C(CH_3)_2\\\vert\\CH_2CO\cdot COOC_2H_5\end{array}$

The compounds obtained by precipitating the substances from the cold solutions of sodium carbonate with acetic acid were represented as possessing the enol form. ~~It~~ They dissolve in alkalies imparting a yellow color to the solution, yield a crystalline copper salt and give immediately a red coloration with alcoholic ferric chloride solution. Heat converts ~~it~~ them into the keto form which is not dissolved by sodium carbonate, gives no red color with ferric chloride solution immediately, and yields no salt with copper acetate. That form which gives metallic salts readily was considered to possess the enol structure; to the other was given the keto structure. Claisen

observed that the equilibrium between the two compounds, i.e., the ratio of enol and keto forms in the same solution, was affected by the solvent used and by the temperature. He found that the transformation of enol to keto form could not be effected by benzene or ligroin. Boiling alcohol acted on the enol form converting one third of it into the keto form, and dilute alcohol increased this conversion.

Wisclecenus'~~s~~ work on formyl-phenyl-acetic ester gave similar results.(1) In certain solutions equilibrium is reached between the two forms present and this equilibrium is directly dependent on three factors, namely, the temperature, concentration and the nature of the solvent used. Wisclecenus brought out the fact that the interconversion of such compounds as these, i.e., of the keto form to the enol form, amounts to nothing more than ~~to~~ a reversible reaction. The work of Michael(2) on the rearrangement and equilibrium of tautomeric acids should also be mentioned.

The difficulties involved in this work on the rearrangements of the thiourazoles can be seen from the following considerations, which have already been discussed in previous articles.(3)



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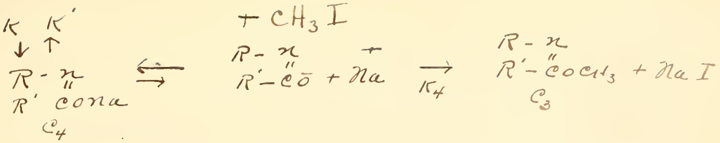
(1) Liebig's Annalen, 291, 1896, 147; Berichte der Deutschen Chemischen Gesellschaft, 32, 2837

(2) Berichte ~~Der~~ der Deutschen Chemischen Gesellschaft, 41, 1080.

(3) American Chemical Journal, 43, 219.



$$\begin{matrix} K & K' \\ \downarrow & \uparrow \end{matrix} \quad \underset{C_4}{\begin{matrix} R-n \\ \| \\ R'\ CONa \end{matrix}} \rightleftarrows \begin{matrix} + CH_3I \\ R-n \quad + \\ \| \\ R'-C\bar{O} + Na \end{matrix} \xrightarrow[K_4]{} \underset{C_3}{\begin{matrix} R-n \\ \| \\ R'-COCH_3 + NaI \end{matrix}}$$

C represents the original concentration of the keto form, C_4 that of the enol form, C_1 the amount of keto salt transformed into enol, C_2 the concentration of the keto ester, and C_3 the concentration of the enol ester. If we have an equimolecular amount of methyl iodide added to a solution containing a mixture of the two salts, we would have the following reactions taking place:

(a) Sodium keto salt $\rightleftarrows$ sodium enol salt.

(b) Sodium enol salt and methyl iodide ⟶ methyl enol ester and sodium iodide.

(c) Sodium keto salt and methyl iodide ⟶ methyl keto ester and sodium iodide.

These would be represented by the differential equations:

$$\frac{dC_1}{dt} = K(C - C_1 - C_2) - K_1(C_4 + C_1 - C_3)$$

$$\frac{dC_2}{dt} = K_2(C - C_1 - C_2)(C + C_4 - C_2 - C_3)$$

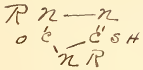
$$\frac{dC_3}{dt} = K_4(C_4 + C_1 - C_3)(C + C_4 - C_2 - C_3)$$

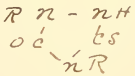
In these equations K is the velocity constant for the

change of the keto salt into the enol salt, K_1 the constant for the reverse rearrangement, K_2 that for the formation of the keto ester, and K_4 that for the formation of the enol ester. The question whether the rearrangement and alkylation reactions of the two tautomeric compounds is molecular or ionic, or both molecular and ionic, is not considered in the above equations.

The possibility that the rearrangement is due to the union of ions in the solution with the molecular forms of the salt or to other complex reactions must also be considered. This work and that previously undertaken by Nirdlinger and Acree (1) however, shows, that the rearrangement of the sodium salt is a reversible monomolecular reaction. These workers have suggested how evidence on the question of abnormal hydrolysis in concentrated solution could be obtained by a study of the slow attainment of equilibrium between the two forms of this weakly acid tautomeric substance.

While working on the various reactions of the thiosemicarbazides, Markwald (2) subjected these substances to the action of phosgene and found that the resulting compounds possessed a certain similarity to the semicarbazides and seemed to be tautomeric. He therefore assigned the following formulae to these compounds, which clearly show their relationship:


I


II

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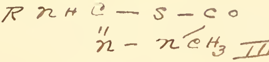
(1) American Chemical Journal, 43, 219.

(2) Berichte der Deutschen Chemischen Gesellschaft, 25, 3098; 29, 2925

From the method of synthesis he was led to believe that the only other possibility would be expressed by the formula

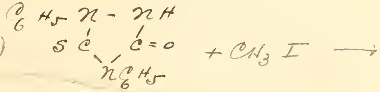


III

This substance however would show basic properties, while in reality the one found had acid properties. If the substance represented by formula I were alkylated it should give a sulphur ester, while that represented by formula II should certainly give a nitrogen ester provided no rearrangement took place during the alkylation.

In 1906 Busch(1) and Reinhardt took up the study of these compounds and arrived at the conclusion that both the sodium 1,4-diphenyl-5-thionurazole, and 1,4-diphenyl-5-thiolurazole reacted with methyl iodide at 100° to form the 1,4-diphenyl-5-thiolmethyl ester. This substance when saponified with potassium hydroxide yielded the potassium salt of the 1,4-diphenylurazole and methyl mercaptan. The course of the reaction according to Busch is:

(a)



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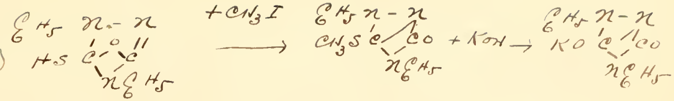
[1] Reinhart's loc. cit. 1906, p. 72

(b)



Busch assumed (b) to be the reactive substance; no action would therefore take place with methyl iodide until sodium 1,4-diphenyl-5-thionurazole was converted into sodium 1,4-diphenyl-5-thiolurazole. At this stage Busch left the work and it was subsequently taken up by Nirdlinger and Acree. (1)

It was indeed found that the sodium salt of 1,4-diphenyl-5-thiolurazole was the more active of the two tautomeric forms but the sodium salt of the 1,4-diphenyl-5-thionurazole is also capable of forming an ester when alkylated with methyl iodide. It was then shown that the sodium salt of 1,4-diphenyl-5-thionurazole yields 1,4-diphenyl-5-thionmethyl ester and that the sodium 1,4-diphenyl-5-thiolurazole yields 1,4-diphenyl-5-thiolmethyl ester, that the 1,4-diphenyl-5-thionurazole and also the sodium salt of 1,4-diphenyl-5-thionurazole could be converted into 1,4-diphenyl-5-thiolurazole and the sodium 1,4-diphenyl-5-thiolurazole. The study of the rearrangement of the sodium salt of 1,4-diphenyl-5-thionurazole into the sodium salt of 1,4-diphenyl-5-thiolurazole and the reverse reaction brought out the fact that the sodium 1,4-diphenyl-5-thiolurazole rearranged about nine times

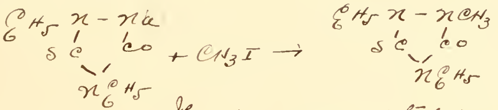
(1) American Chemical Journal, 43, 719;

as fast as the sodium 1,4-diphenyl-5-thionurazole under the same conditions. Busch,(1) who conducted his work ~~on~~ by qualitative methods, affirmed the correctness of the view held by Nirdlinger and Acree regarding the structure of the tautomeric compounds and the esters obtained.

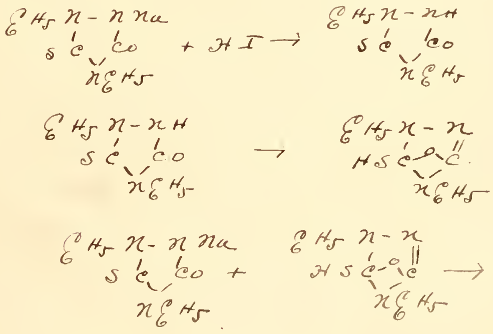
In determining the ratio of 1,4-diphenyl-5-thionurazole to 1,4-diphenyl-5-thiolurazole in a mixture, the salts were alkylated and the ratio of esters was used to express the amount of each form present in the original mixture. Since the rearrangement of one salt into the other is slow, in comparison with the rate of alkylation in a neutral solution, this is permissible. It was found by Markwald and Busch and also by Nirdlinger and Acree that in slightly acid alcoholic solutions the 1,4-diphenyl-5-thionurazole rapidly rearranged to form the 1,4-diphenyl-5-thiolurazole. Since the alkylations were effected by equimolecular amounts of sodium hydroxide and 1,4-diphenyl-5-thionurazole to form the sodium salt of 1,4-diphenyl-5-thionurazole, the solution at the beginning of the reaction was neutral. During the alkylation, however, the hydriodic acid formed from the hydrolysis of the methyl iodide reacted with the sodium 1,4-diphenyl-5-thionurazole to form 1,4-diphenyl-5-thionurazole and sodium iodide. In the alcoholic solution the 1,4-diphenyl-5-thionurazole rearranged into 1,4-diphenyl-5-thiolurazole. The 1,4-diphenyl-

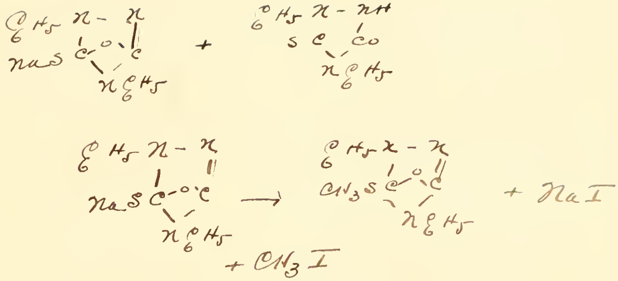
(1) Berichte der Deutschen Chemischen Gesellschaft, 42, 476

5-thiolurazole, being the stronger acid, formed the sodium salt of 1,4-diphenyl-5-thiolurazole, at the same time liberating 1,4-diphenyl-5-thionurazole which then rearranged. The results obtained from alkylations conducted by means of methyl iodide in alcoholic solution on the sodium 1,4-diphenyl-5-thionurazole must necessarily show a higher per cent of sodium 1,4-diphenyl-5-thiolurazole, if the ratio of esters is used to determine the ratio of sodium 1,4-diphenyl-5-thionurazole and sodium 1,4-diphenyl-5-thiolurazole in the original compound. The following reactions will help to make this clear:



If no rearrangement took place

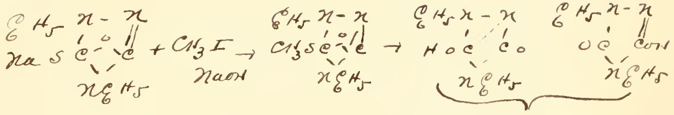


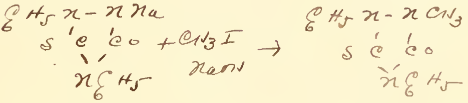


This then shows why alkylations with methyl iodide in alcoholic solution gave no pure 1,4-diphenyl-5-thionmethyl ester from the pure sodium 1,4-diphenyl-5-thionurazole. The sodium salts of 1,4-diphenyl-5-thionurazole and 1-4-diphenyl-5-thiolurazole should therefore not yield the theoretical per cent of ester. This indeed was found to be the case.

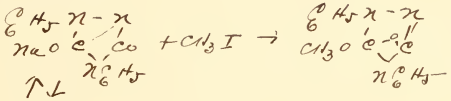
The addition of a slight excess of sodium hydroxide to the alkylation mixture of the sodium salt of 1,4-diphenyl-5-thionurazole showed this compound to be free from any thiol form -- the thion ester is not affected by potassium hydroxide at 60°. When an excess of sodium hydroxide, however, was added to a mixture of the sodium 1,4-diphenyl-5-thionurazole and sodium 1,4-diphenyl-5-thiolurazole and this mixture was alkylated the methyl ester formed from

the methyl iodide and sodium 1,4-diphenyl-5-thiolurazole was partially saponified. The following may help to explain this reaction:

(c)


(d)


The ester formed in (d) is not affected by sodium hydroxide, but the 1,4-diphenyl-5-methylthiolurazole is very sensitive to the action of sodium hydroxide and is converted into the sodium salt of the 1,4-diphenylurazole, as shown in equation (c). The methyl iodide can react further with the sodium salt of 1,4-diphenylurazole to form the 1,4-diphenyl 3-or 5-methoxy or 2-N-ester, as expressed in the following equations:

I


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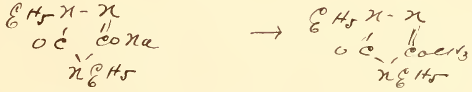

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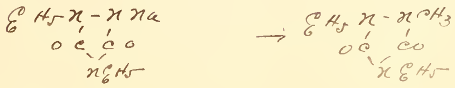
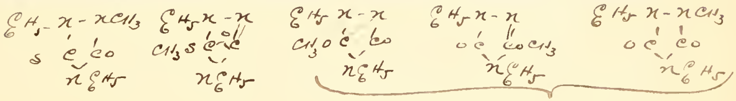


The esters I, II and III would be extracted with the esters of 1,4-diphenyl-5-thionmethylurazole and would make the estimation of this ester inaccurate. The per cent of the methyl 1,4-diphenyl-5-thiolurazole is therefore low. The esters obtained when a mixture of the sodium salts is alkylated with methyl iodide would be represented thus:



On alkylating sodium 1,4-diphenyl-5-thionurazole with methyl iodide in alcohol solution we would not expect to get an amount of 1,4-diphenyl-5-thionmethyl ester equal to the original sodium salt used, but an ester composed of 1,4-diphenyl-5-thiolmethyl ester and 1,4-diphenyl-5-thionmethyl ester.

In order to study the rearrangements of the sodium 1,4-diphenyl-5-thionurazole by the ratio of the methyl ester of each tautomer found, a method of alkylation must be adopted which maintains the solution practically neutral and prevents the rearrangement of 1,4-diphenyl-5-thionurazole into 1,4-diphenyl-5-thiolurazole, and also the saponification of the 1,4-diphenyl-5-thiolmethyl ester formed, during the alkylation. To secure these conditions a solution consist-

ing of disodium acid phosphate and sodium acid phosphate in the proportion of 1 part monosodium phosphate to 1 part of disodium phosphate has been used successfully; the details are discussed in the experimental portion. By the use of such a method I have succeeded in showing that the 1,4-diphenyl-5-thionurazole and its salts can be changed into 1,4-diphenyl-5-thiolurazole and the corresponding salts. But the reaction is never complete, not over about 61.5 per cent of the sodium 1,4-diphenyl-5-thionurazole being changed into the sodium 1,4-diphenyl-5-thiolurazole. Whether the reaction is reversible or whether the so-called sodium 1,4-diphenyl-5-thionurazole is changed into an equilibrium mixture of sodium 1,4-diphenyl-5-thiolurazole and an isomer which behaves essentially like the original sodium 1,4-diphenyl-5-thionurazole is not clear from the data. For the sake of simplicity I have assumed the reaction to be reversible and shall continue the work in order to try in the future to clear up these uncertainties.

EXPERIMENTAL.

Phenyl Mustard Oil:

The yield of phenyl mustard oil made according to the method described in Gatterman's "Praxis des Organischen Chemikers"never exceeded 40 per cent. Since the mustard oil was used in large quantities in these experiments some time was spent in trying to ~~perfect~~ the method. It was found that if the thiocarbanilid from which the mustard oil is made by hydrolysis with concentrated hydrochloric acid is thoroughly dried the yield can be doubled, if the following directions are complied with; After the required amount of hydrochloric acid has been added to the flask containing the thiocarbanilid the mixture is heated until the phenyl mustard oil formed separates and shows its presence by floating on the surface of the liquid. Steam is then passed through the flask until all mustard oil has been driven out. Its subsequent treatment was the same as that given in Gatterman's "Praxis des Organischen Chemikers." In one case 95 per cent of the theoretical yield was obtained; while no experiment gave a yield less than 85%. Again, the time consumed in conducting an experiment is one third of that required by Gatterman's method.

2,4-Diphenyl-3-thiosemicarbazide.

The method followed for the preparation of this com-

pound was that of Busch and Holzman.(1) It was purified by recrystallization from boiling benzene.. It melted sharply at 144°, rearranged and melted again at 212°. It remained perfectly white, when left in contact with the air. From 20 grams of phenylhydrazine 15 grams of the pure semicarbazide were obtained.

1,4-Diphenyl-5-thionurazole:

The compound was made by the method of Busch and Reinhardt.(2) The method followed has already been described by Nirdlinger and Acree.(3) It melted at 144°, rearranged and melted at 220°. The solution of the sodium salt possessed a yellowish tinge while that obtained from the impure semicarbazide was perfectly colorless. All attempts to purify the urazole by recrystallization were unsuccessful. The tendency to rearrange was so great that even at 40°C. the substance was transformed to the higher melting tautomer. This substance was used in an attempt to make the pure thiolurazole.

1,4-Diphenyl-5-thiolurazole:

All attempts to obtain this substance in pure condition proved unsuccessful. Experiments were conducted under conditions thought to be most favorable for its formation but none of these yielded a compound of higher than 60 per cent purity. The following methods were used to

(1) Berichte der Deutschen Chemischen Gesellschaft, 34, 324
Holzmann: Diss., Erlangen, 1902.
(2) Reinhardt: Diss., p.66.
(3) American Chemical Journal, 43, 219.

isolate the pure substance. First, since the thionurazole is the weaker acid, it was thought that carbonic acid might precipitate it from a mixture of the sodium salts of the two acids. Carbonic acid, however, precipitated neither acid from its sodium salt at ordinary temperatures. Second, if the melting points of the individual tautomers can be used as a criterion of purity, the rearrangement into the thiolurazole might be effected by heating the thionurazole to 220°. Experiments, however, in which a temperature of 210° was maintained for 30 minutes gave no substance purer than 60 per cent thiolurazole. Busch (1) states that the thionurazole can be entirely separated from the thiolurazole by treating a mixture of the sodium salts with acetic acid, but this acid precipitated by this method was found to be a mixture of the two tautomeric forms and not one individual. Finally, it was thought that potassium sulphhydrate might be used to saponify the 1,4-diphenyl-5-thiolmethyl ester and yield the pure potassium thiolurazole and methyl sulfhydrate. The substance obtained melted at 141°, and not at 220°.

Methyl Thiol Ester of 2,4-Diphenyl-3-thiosemicarbazide:

This substance was made according to the method of Busch and Wolpert.(2) To 28 grams finely divided 2,4-diphenyl-3-thiosemicarbazide were added 6.5 grams of caustic

(1) Berichte der Deutschen Chemischen Gesellschaft, 42, 4763
(2) " " " " " 34, 335

potash dissolved in 58 grams of 90 per cent alcohol. The solution was warmed slightly in order to accelerate the formation of the potassium salt. To this was then added 17 grams of methyl iodide and the solution was placed in salt and ice and allowed to stand an hour. The percipitate was filtered, washed with cold water and recrystallized from alcohol. The crystals assumed a red color, but this was removed by frequent washings with cold alcohol. The substance obtained was pure white and melted sharply at 78°.

Methyl Thiol Ester of 1,4-Diphenyl-5-thiolurazole:

This ester was made as described by Busch and Wolpert.(1) To 30 grams of a 20 per cent solution of phosgene in toluene, were added 7 grams of the methylthiosemicarbazid in 20 grams of benzene. Both solutions were cooled in a mixture of salt and ice and the resulting solution was allowed to stand in this mixture one hour. The thiolurazole ester was then filtered off and recrystallized from alcohol. The substance was perfectly white and while still moist melted at 178°-180°C. After it was thoroughly dried in a vacuum dessicator over sulphuric acid it melted sharply at 196°C. Five grams of substance were obtained. The amount of water or alcohol held by the ester amounted to 25 per cent of the total weight. The following table shows the gradual loss of

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(1) Berichte der Deutschen Chemischen Gesellschaft, 34, 340.

this water at 70° and the consequent rise in melting point.

Weight of Dish.	Weight of Dish and Ester.	Time Heated: Hours.	M. Pt.
23.9747	27.0977	0	178°-180°
	26.3176	1.5	184°-185°
	26.3169	3.00	194°-196°
	26.3169	4.5	196°

Method of Alkylation of the 1,4-Diphenyl-5-thionurazole:

The alkylation of the pure sodium salt of the thion acid with methyl iodide in the presence of alcohol gives a mixture of thion and thiol esters. If, on the other hand, the alkylation is carried out without the use of alcohol pure thion ester is obtained. The odor of mercaptan was noticed in both cases. It is probable, therefore, that some of the thiol ester formed had been converted into the 1,4-diphenyl-3- or 5-methoxyurazole. For this reason, alkylations were carried out in the presence of disodium acid phosphate and monosodium acid phosphate, 50% of Na_2HPO_4 and 50% of NaH_2PO_4. If the sodium phosphates are not used, any hydriodic acid formed by the hydrolysis of the methyl iodide would act on the sodium salt liberating the 1,4-diphenyl-5-thionurazole. This would then, in the pres-

ence of alcohol rearrange immediately into the 1,4-diphenyl-5-thiol acid. The 1,4-diphenyl-5-thiolurazole, being the stronger acid, would act on the sodium salt of the 1,4-diphenyl-5-thionurazole to form the sodium salt of 1,4-diphenyl-5-thiolurazole and the 1,4-diphenyl-5-thion acid. The 1,4-diphenyl-5-thion acid thus formed would rearrange; while the sodium salt of the 1,4-diphenyl-5-thiolurazole would be alkylated. In this way a higher per cent of the 1,4-diphenyl-5-thiol ester is obtained with the use of alcohol than without it.

The use of the phosphate mixture in the proportions shown above wholly avoids the formation of any free thion acid. The method is accurate to within 4 or 5 per cent. The method of procedure is as follows:

To 0.1204 grams of pure 1,4-diphenyl-5-thionurazole weighed out in a tube sealed off at one end there was added 0.98 c.c. of a 0.5 normal solution of sodium hydroxide. After the acid had gone into solution 0.45 c.c. of 0.5 N sodium hydroxide and 0.27 c.c. of 1.5 N phosphoric acid were added thereby forming a mixture consisting of one mol of $Na_2H\ PO_4$ and one mol of NaH_2PO_4. In order to avoid the precipitation of the urazole by phosphoric acid the tube was drawn out to a fine capillary at the one end and the sodium

hydroxide and phosphoric acid first mixed in the part of the tube above the capillary. Then by alternately warming and cooling the air space above the solution of the sodium salt the phosphate mixture can be drawn into the lower section without effecting any precipitation whatever. To this solution there was then added 0.58 c.c. methyl iodide, and the tube was sealed off and heated with constant shaking in a bath at 60°C. It was then cooled in ice, opened and the contents transferred to an extraction funnel containing water, to which a little sodium hydroxide had been added. The ester was extracted with 6 successive portions of chloroform and the chloroform was run into a weighed porcelain dish on a hot water bath and evaporated below its boiling point. The dish was transferred to a vacuum dessicator for 24 hours and then weighed. After the first 24 hours the weight remained constant. A dish allowed to stand 6 days showed no change in weight. The ester obtained is pale lemon yellow and is of syrupy consistency. It crystallized from solution in alcohol as a white powder which melted at 94°C. This substance is the nitrogen ester.

Hydrolysis of Esters: Separation of the Thiol and Thion Methyl Esters of 1,4-Diphenyl-5-Thiourazole:

Nirdlinger and Acree (1) showed that the separation of the thion ester of 1,4-diphenyl-5-thiourazole could be ef-

(1) American Chemical Journal, 4[illegible], [illegible]

fected by digesting them with concentrated alkalies. The method adopted follows:

The weighed esters were carefully transferred by the use of no more than one cubic centimeter of chloroform to a tube sealed at one end. In this way the bumping which occurs in blowing off an excess of chloroform can be avoided. The solution was then treated with 5 c.c. of a 0.5 N solution of sodium hydroxide, the tube was sealed off and placed in the constant temperature bath at 60°, and was shaken for 1.5 hours. It was then taken out of the bath, cooled, opened, its contents transferred to an extraction funnel containing water to which a few drops of alkali had been added, extracted with chloroform and weighed in the usual manner. This process saponified the 1,4-diphenyl-5-methylthiolurazole and left the methyl 1,4-diphenyl-5-thionurazole unchanged.

Hydrolysis of Thion Ester: Separation of the N- from the O-ester.

The method at first used to effect this separation was the following:- The mixture of esters was treated with a solution of alcoholic hydrochloric acid. The results, however, were not good owing to the fact that for some reason the ester (nitrogen ester) volatilized with the chloroform. The final method follows:

The thion esters obtained from saponification were transferred by means of chloroform to a tube drawn out at one

end. Five c.c. of a concentrated aqueous solution of hydrochloric acid was added, the tube sealed off, placed in a constant temperature bath at 60° and shaken for 1.5 hours. It was then taken out of the bath, cooled in ice water and opened. The contents were then transferred to an extraction funnel containing water. Concentrated alkali~~e~~ was then added to neutralize the excess of hydrochloric acid, and the ester was extracted from alkaline solution with chloroform. The chloroform extract was transferred to a weighed dish, the chloroform blown off carefully on the water bath with a current of air, the temperature of the water bath not exceeding 70°, the dish put in a vacuum desiccator, dried and weighed. The following data shows that the ester and acid are completely extracted by 6 such extractions:

Ester Mixture	N. Ester	O. Acid
0.0297 gms.	0.0230 gms.	0.0089 gms.
0.0384 "	0.0270 "	0.0125 "

That the ester obtained is practically non-volatile in vacuo is shown by the following data: A moist ester amounting to 0.1010 grams lost but 4 per cent in weight in 21 hours in vacuo and then the weight remained constant.

Analysis of Thion Nitrogen Esters:

The esters obtained from the rearrangement experiments on recrystallization from alcohol yielded a white powder which melted at 94°, and was identical with that obtained by Nirdlinger and Acree from the sodium salt of 1,4-diphenyl-5-thionurazole. It contained sulphur. An analysis ~~using~~ of 0.1401 grams urazole gave 0.1342 grams $BaSO_4$ or 11.21 per cent sulphur, the theoretical being 11.91 per cent. The acid formed by hydrolysis melted at 128°-130° and is probably the 1,4-diphenylurazole. The amount obtained was so small however that the attempt to identify the substance was abandoned.

The Rearrangement of the Sodium 1,4-Diphenyl-5-thionurazole into the Sodium 1,4-Diphenyl-5-thiolurazole.

A weighed amount of urazole was placed in a tube constricted at one end. To this was then added the theoretical amount of 0.5 N sodium hydroxide. The tube was then sealed off and placed in the bath at 60° and allowed to rearrange over a definite time period. It was then removed from the bath, opened, and the proper amounts of sodium hydroxide, phosphoric acid and methyl iodide added. After alkylation, the esters were extracted from the contents of the tube, weighed and hydrolyzed as described. The loss in ester from the total ester obtained corresponded to the methyl thiol ester hy-

drolyzed. The nitrogen and oxygen esters were then transferred to a tube and there hydrolyzed with hydrochloric acid. The difference between the mixture of esters and the final ester gives the amounts of oxygen ester in the original mixture. The curve shows the gradual rearrangement from thion acid to thiol acid, the ordinates representing time periods and the absciscae the amount of change of sodium thionurazole into sodium thiolurazole.

The experiments were carried out in aqueous solution without the use of alcohol.

Time Hours	Weight Urazoles	Total Weight Esters	Weight of N- and O-Esters	Per cent Rearranged	Weight of N-Esters
	gms.	gms.	gms.		gms.
2	1226	1242	1142) (	10	1138
2	1310	1317	1159)	10	1103
4	1189	1195	1016	15	.0942
6	1387	1423	1124	20.9	------
12	.1265	.1333	1025	24	.0984
72	.1623	1776	1110	37.5	.1009
96	.0885	.0937	.0537	43	.0484

Time Hours	Weight of Urazole	Total Weight Esters	Weight N- and O-Esters	Per cent Na salt Rearranged	Weight of N-Ester
168	.0998	.1111	.0582	47.6	.0544
240	.1123	.1209	.0619	51.2	-----
504	.1592	.1676	.1031	61.5	-----

In the next series the alkylation mixture consisted of methyl iodide in a 40% alcohol solution--the same sodium phosphate and disodium acid phosphate mixture being used in these experiments as in the foregoing series.

Time Hours	Urazole	Total Ester	N- and O-Esters	Per cent Na Urazole Rearranged
(6)	(.0862)	(.0910)	(.0666)	(26)
12	.1156	.1194	.0957	20
72	.1126	.1251	.0736	41
96	.1134	.1249	.0620	51
168	.1324	.1392	.0556	60
240	.1094	.1150	.0367	68

If this reaction is monomolecular we would have:

$$\frac{dc_2}{dt} = K_1(C - C_2) - K_2(C_1 + C_2),$$

in which C is the original concentration of the sodium 1,4-diphenyl-5-thionurazole, C_1 that of the 1,4-diphenyl-5-thiolurazole present at first, and C_2 that of the rearranged salt. When equilibrium is reached

$$\frac{K_1}{K_2} = \frac{C_1 + C_2}{C - C_2}.$$

If we substitute $\frac{K_1}{K_2} = K$ in the first equation and integrate we get

$$K_1 + K_2 = \frac{1}{t} \log \frac{KC - C_1}{KC - C_1 - (K+1)C_2}$$

C in the experiments above is equal to 100.00, and C_1 is 0.00. The value for C_2 over a time period of 900 hours is equal to 1.60; this therefore is taken as the equilibrium ratio.

K therefore equals 1.60, as is seen from the equation

$$k = \frac{0.00 + 61.5}{100 - 61.5} = \frac{61.5}{38.5} = 1.60$$

Time Hours	C	C_1	C_2	K_1+K_2	K_2	K_1
2	100	0.00	10.00	.0038	.0024	.0014
4	100	0.00	15.00	.0030	.0019	.0011
6	100	0.00	20.9	.0030	.0019	.0011
12	100	0.00	24.0	(.0018)	(.0011)	(.0007)
72	100	0.00	37.5	.0056	.0034	.0022
96	100	0.00	43.0	.0055	.0034	.0021
168	100	0.00	47.6	.0038	.0024	.0012
504	100	0.00	61.5	.0040	.0025	.0015

Since the equation gives a fairly good constant the reaction

may be assumed at present to be monomolecular and reversible.

Hydrolyses of Esters Formed by Alkylation in 40 Per Cent Alcohol.

These dishes were left in a desiccator over the summer months and were taken out for hydrolysis the following fall. The ratio of N-ester to O-ester found varies with the time period over which the original sodium salt was allowed to rearrange:

	Time hours	Weight of Total N- and O-ester	Weight of Unhydrolyzed or N-ester	Per Cent Hydrolyzed
1-	0	.1934	.1815	6%
2-	6	.1800	.1611	11%
3-	24	.1410	.1269	19%
4-	72	.0795	.0625	23%
5-	96	.0556	.0438	26%
6-	168	.0384	.0270	30%
7-	216	.0343	.0180	52%
8-	336	.0204	.0112	55%

The N-ester melted at 94°.

Evidence in Favor of Rearrangement of 1,4-Diphenyl-5-Thiol-Urazole into 1,4-Diphenyl-5-Thionurazole:

Although the pure 1,4-diphenyl-5-thiolurazole was not obtained, the following experiments show that such rearrangement does take place. The pure methyl ester of 1,4-diphenyl-5-thiolurazole treated with potassium sulphhydrate does not yield pure 1,4-diphenyl-5-thiolurazole but a compound melting at 142° which is the melting point of the 1,4-diphenyl-5-thionurazole. Again, experiments which were carried out with the use of diazo-methane in ether solution yielded the following results:

Weight of 1,4-Diphenyl-5-thiolurazole (60% pure) percent	Weight of Ester not Hydrolyzed by KOH
.0801	.0801

Weight of 1,4-Diphenyl-5-thion Acid	Weight Thion Ester from CH_2N_2	Weight Thion Ester not Hydrolyzed by KOH
0.1271	0.1255	0.1253

This shows that almost the entire thiol acid has been converted into thion ester--in other words the reaction is reversible as follows:

1,4-Diphenyl-5-thionurazole $\rightleftarrows$ 1,4-diphenyl-5-thiolurazole.

Silver Salt of 1,4-Diphenyl-5-Thionurazole:

The sodium salt of 1,4-diphenyl-5-thionurazole dissolved in water was treated with silver nitrate in aqueous solution until no further precipitation took place. The precipitate

was then filtered off, washed several times with water and dried on a clay plate.

Alkylation of Silver 1,4-Diphenyl-5-Thionurazole:

Owing to the fact that during the alkylation some silver iodide was formed which occluded some of the silver salt and prevented its alkylation, no theoretical yield of ester could be obtained. The following experiments, however, show plainly that the three tautomeric forms are present and that they exist in different ratio than had been obtained from the sodium 1,4-diphenyl-5-thionurazole. Attempts to alkylate the silver salt to completion over long time periods were unsuccessful and such attempts furthermore increased the possibilities for rearrangement during the alkylation. The following data shows this rearrangement:

Time hours	Ag Salt	Total Ester: 1,4-Diphenyl-5-thiol-methyl ester and 1,4-Diphenyl-5-thion methyl ester.	N-ester and O-ester	N-ester
3	.2921	.0859	.0824	.0804
3	.1755	.0603	.0470	.0436

Barium Salt of 1,4-Diphenyl-5-thionurazole:

To the sodium salt of 1,4-diphenyl-5-thionurazole was

added an excess of barium hydroxide; the solution was then placed in ice until all the barium salt had been precipitated. The barium salt was then filtered out, washed with cold water and dried in the usual manner.

Alkylation of Barium, 1,4-Diphenyl-5-thionurazole:

Since the barium salt is insoluble in water no theoretical yield of ester could be obtained. It was found, however, that the ratios of the two tautomeric modifications in the barium salt differed from those in the silver and sodium salts of 1,4-diphenyl-5-thionurazole. The following results were obtained:

Hours.	Amount Salt.	Ester.	Ester not Hydrolyzed by KOH: N-ester and O-ester.	Ester not Hydrolyzed by HCl: N-ester.
3/4	.2986	.0478	.0407	.0376
1 1/2	.4500	.3213	.2855	.2787

Biography.

Ernest Pohl Doetsch, the author of this dissertation, was born in Baltimore, Maryland, September 18, 1884. His early education was obtained in the public schools of Baltimore and in Deichmann's Preparatory School, from which he graduated in June, 1903. He then entered Johns Hopkins University and graduated in 1907 with the degree of A.B. In the fall of 1907 he entered the graduate department of Johns Hopkins University as a graduate student in Chemistry, with Physical Chemistry and Economic Geology as his subordinate subjects.